CLAIMS

What is claimed is:

1. A method of treating and/or preventing a vascular disease characterized by nitric oxide insufficiency in a patient in need thereof comprising administering a therapeutically effective amount of at least one nitrosated angiotensin-converting enzyme inhibitor, nitrosated beta-adrenergic blocker, nitrosated cholesterol reducer, nitrosated calcium channel blocker, nitrosated angiotensin II receptor antagonist, nitrosated endothelin antagonist, nitrosated renin inhibitor, or a mixture of two or more thereof.

2. The method of claim 1, further comprising administering a pharmaceutically acceptable carrier.

3. The method of claim 1, wherein the vascular disease characterized by nitric oxide insufficiency is a cardiovascular disease; a disease resulting from oxidative stress; low-renin hypertension; salt-sensitive hypertension; low-renin, salt-sensitive hypertension; primary pulmonary hypertension; thromboembolic pulmonary hypertension; pregnancy-induced hypertension; renovascular hypertension; hypertension-dependent end-stage renal disease; heart failure; microvascular cardiac ischemia; left ventricular hypertrophy with disproportionate microvascularization or diastolic dysfunction.

4. The method of claim 3, wherein the cardiovascular disease is congestive heart failure, hypertension, pulmonary hypertension, myocardial infarction, cerebral infarction, atherosclerosis, atherogenesis, thrombosis, ischemic heart disease, post-angioplasty restenosis, coronary artery diseases, renal failure, stable, unstable or variant (Prinzmetal) angina, cardiac edema, renal insufficiency, nephrotic edema, hepatic edema, stroke, transient ischemic attack, cerebrovascular accident, restenosis, controlling blood pressure in hypertension, platelet adhesion, platelet aggregation, smooth muscle cell proliferation, vascular complication associated with the use of medical device, wound associated with the use of medical device, pulmonary thromboembolism, cerebral thromboembolism, thrombophlebitis, thrombocytopenia or bleeding disorder.

5. The method of claim 4, wherein the cardiovascular disease is congestive heart failure, hypertension, restenosis or atherosclerosis.

6. The method of claim 3, wherein the disease resulting from oxidative stress is

atherogenesis, atheromatosis, arteriosclerosis, artherosclerosis, vascular hypertrophy associated with hypertension, hyperlipoproteinaemia, normal vascular degeneration through aging, parathyroidal reactive hyperplasia, chronic renal disease, a neoplastic disease, an inflammatory disease, a neurological and acute bronchopulmonary disease, tumorigenesis, ischemia-reperfusion syndrome, arthritis or sepsis.

7. The method of claim 1, wherein the at least one nitrosated angiotensin-converting enzyme inhibitor, nitrosated beta-adrenergic blocker, nitrosated cholesterol reducer, nitrosated calcium channel blocker, nitrosated angiotensin II receptor antagonist, nitrosated endothelin antagonist, nitrosated renin inhibitor, or mixture of two or more thereof are in the form of a pharmaceutically acceptable salt.

8. The method of claim 1, wherein the at least one nitrosated angiotensin-converting enzyme inhibitor, nitrosated beta-adrenergic blocker, nitrosated cholesterol reducer, nitrosated calcium channel blocker, nitrosated angiotensin II receptor antagonist, nitrosated endothelin antagonist, nitrosated renin inhibitor, or mixture of two or more thereof, are orally administered as a solid dose.

9. The method of claim 8, wherein the solid dose is a tablet or a capsule.

10. The method of claim 9, wherein the tablet is a sustained release tablet or the capsule is a sustained release capsule.

11. The method of claim 1, wherein the nitrosated angiotensin-converting enzyme inhibitor is a nitrosated alacepril, a nitrosated benazepril, a nitrosated captopril, a nitrosated ceronapril, a nitrosated cilazapril, a nitrosated delapril, a nitrosated duinapril, a nitrosated enalapril, a nitrosated enalaprilat, a nitrosated fosinopril, a nitrosated imidapril, a nitrosated lisinopril, a nitrosated moveltipril, a nitrosated naphthopidil, a nitrosated pentopril, a nitrosated perindopril, a nitrosated quinapril, a nitrosated ramipril, a nitrosated rentipril, a nitrosated spirapril, a nitrosated temocapril, a nitrosated trandolapril, a nitrosated urapidil or a nitrosated zofenopril.

12. The method of claim 1, wherein the nitrosated beta-adrenergic blocker is a nitrosated acebutolol, a nitrosated alprenolol, a nitrosated amosulalol, a nitrosated arotinolol, a nitrosated atenolol, a nitrosated betaxolol, a nitrosated bethanidine, a nitrosated bevantolol, a nitrosated bisoprolol, a nitrosated bopindolol, a nitrosated bucumolol, a nitrosated bufetolol, a

nitrosated bufuralol, a nitrosated bunitrolol, a nitrosated bupranolol, a nitrosated butafilolol, a nitrosated carazolol, a nitrosated carteolol, a nitrosated carvedilol, a nitrosated celiprolol, a nitrosated cetamolol, a nitrosated dilevalol, a nitrosated epanolol, a nitrosated esmolol, a nitrosated indenolol, a nitrosated labetalol, a nitrosated mepindolol, a nitrosated metipranolol, a nitrosated metoprolol, a nitrosated moprolol, a nitrosated nadolol, a nitrosated nadoxolol, a nitrosated nebivolol, a nitrosated nifenalol, a nitrosated nipradilol, a nitrosated oxprenolol, a nitrosated penbutolol, a nitrosated pindolol, a nitrosated practolol, a nitrosated pronethalol, a nitrosated propranolol, a nitrosated sotalol, a nitrosated sulfinalol, a nitrosated talinolol, a nitrosated tertatolol, a nitrosated tilisolol, a nitrosated timolol, a nitrosated toliprolol or a nitrosated xibenolol,

13. The method of claim 1, wherein the nitrosated cholesterol reducer is a nitrosated HMG-CoA reductase inhibitor, a nitrosated sequestrant or a nitrosated inhibitor of cholesterol absorption.

14. The method of claim 13, wherein the nitrosated HMG-CoA reductase inhibitor is a nitrosated lovastatin, a nitrosated simvastatin, a nitrosated pravastatin, a nitrosated fluvastatin, a nitrosated cerivastatin or a nitrosated atorvastatin.

15. The method of claim 13, wherein the nitrosated sequestrant is a nitrosated cholestyramine, a nitrosated colestipol or a nitrosated alkylaminoalkyl derivatives of cross-linked dextran.

16. The method of claim 13, wherein the nitrosated inhibitor of cholesterol absorption is a nitrosated beta-sitosterol, a nitrosated acyl CoA-cholersterol acyltransferase inhibitor or a nitrosated melinamide.

17. The method of claim 1, wherein the nitrosated calcium channel blocker is a nitrosated amlodipine, a nitrosated aranidipine, a nitrosated barnidipine, a nitrosated benidipine, a nitrosated cilnidipine, a nitrosated clentiazem, a nitrosated diltiazen, a nitrosated efonidipine, a nitrosated fantofarone, a nitrosated felodipine, a nitrosated isradipine, a nitrosated lacidipine, a nitrosated lercanidipine, a nitrosated manidipine, a nitrosated mibefradil, a nitrosated nicardipine, a nitrosated nifedipine, a nitrosated nilvadipine, a nitrosated nisoldipine, a nitrosated nitrendipine, a nitrosated semotiadil or a nitrosated veraparmil.

18. The method of claim 1, wherein the nitrosated angiotensin II receptor antagonist

is a nitrosated ciclosidomine, a nitrosated eprosartan, a nitrosated furosemide, a nitrosated irbesartan, a nitrosated losartan, a nitrosated saralasin or a nitrosated valsartan.

19. The method of claim 1, wherein the nitrosated endothelin antagonist is a nitrosated bosentan, a nitrosated sulfonamide endothelin antagonists, a nitrosated BQ-123 or a nitrosated SQ 28608.

20. The method of claim 1, wherein the nitrosated renin inhibitor is a nitrosated enalkrein, a nitrosated RO 42-5892, a nitrosated A 65317, a nitrosated CP 80794, a nitrosated ES 1005, a nitrosated ES 8891 or a nitrosated SQ 34017.

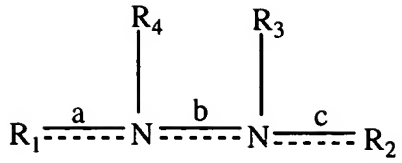
21. The method of claim 1, further comprising administering to the patient a therapeutically effective amount of at least one compound used to treat a cardiovascular disease or a pharmaceutically acceptable salt thereof.

22. The method of claim 21, wherein the compound used to treat the cardiovascular disease is an angiotensin-converting enzyme inhibitor, a beta-adrenergic blocker, a cholesterol reducer, a calcium channel blocker, an angiotensin II receptor antagonist, an endothelin antagonist, a renin inhibitor, or a mixture of two or more thereof.

23. The method of claim 1, further comprising administering to the patient a therapeutically effective amount of at least one antioxidant or a pharmaceutically acceptable salt thereof and/or a therapeutically effective amount of at least one compound that donates, transfers, or releases nitric oxide, or induces the production of endogenous nitric oxide or endothelium-derived relaxing factor or is a substrate for nitric oxide synthase or a pharmaceutically acceptable salt thereof.

24. The method of claim 23, wherein the antioxidant is a small-molecule antioxidant, or a pharmaceutically acceptable salt thereof, or an antioxidant enzyme.

25. The method of claim 24, wherein the small-molecule antioxidant is a compound of formula (I), a glutathione, a vitamin C, a vitamin E, a cysteine, a N-acetyl-cysteine, a β-carotene, an ubiquinone, an ubiquinol-10, a tocopherol, a coenzyme Q, or a mixture of two or more thereof; wherein the compound of formula (I) is:



(I)

wherein a, b and c are independently a single or double bond; R_1 and R_2 are each independently a hydrogen, an alkyl, an ester or a heterocyclic ring; R_3 and R_4 are each independently a lone pair of electrons or a hydrogen; with the proviso that at least one of R_1, R_2, R_3 and R_4 is not a hydrogen.

26. The method of claim 23, wherein the antioxidant enzyme is a superoxide dismutase, a catalase, a glutathione peroxidase, or a mixture of two or more thereof.

27. The method of claim 25, wherein the compound of formula (I) is budralazine, cadralazine, dihydralazine, endralazine, hydralazine, pildralazine, todralazine or a pharmaceutically acceptable salt thereof.

28. The method of claim 25, wherein the compound of formula (I) is hydralazine hydrochloride.

29. The method of claim 23, wherein the at least one compound that donates, transfers, or releases nitric oxide, or induces the production of endogenous nitric oxide or endothelium-derived relaxing factor or is a substrate for nitric oxide synthase is an S-nitrosothiol.

30. The method of claim 29, wherein the S-nitrosothiol is S-nitroso-N-acetylcysteine, S-nitroso-captopril, S-nitroso-N-acetylpenicillamine, S-nitroso-homocysteine, S-nitroso-cysteine, S-nitroso-glutathione or S-nitroso-cysteinyl-glycine.

31. The method of claim 29, wherein the S-nitrosothiol is:

(i) $HS(C(R_e)(R_f))_mSNO$;

(ii) $ONS(C(R_e)(R_f))_mR_e$; and

(iii) $H_2N\text{-}CH(CO_2H)\text{-}(CH_2)_m\text{-}C(O)NH\text{-}CH(CH_2SNO)\text{-}C(O)NH\text{-}CH_2\text{-}CO_2H$;

wherein m is an integer from 2 to 20; R_e and R_f are each independently a hydrogen, an alkyl, a cycloalkoxy, a halogen, a hydroxy, an hydroxyalkyl, an alkoxyalkyl, an arylheterocyclic ring, an alkylaryl, a cycloalkylalkyl, a heterocyclicalkyl, an alkoxy, a haloalkoxy, an amino, an alkylamino, a dialkylamino, an arylamino, a diarylamino, an alkylarylamino, an alkoxyhaloalkyl,

a haloalkoxy, a sulfonic acid, a sulfonic ester; an alkylsulfonic acid, an arylsulfonic acid, an arylalkoxy, an alkylthio, an arylthio, a cycloalkylthio, a cycloalkenyl, a cyano, an aminoalkyl, an aminoaryl, an aryl, an arylalkyl, an alkylaryl, a carboxamido, a alkylcarboxamido, an arylcarboxamido, an amidyl, a carboxyl, a carbamoyl, a carbamate, an alkylcarboxylic acid, an arylcarboxylic acid, an alkylcarbonyl, an arylcarbonyl, an ester, a carboxylic ester, an alkylcarboxylic ester, an arylcarboxylic ester, a haloalkoxy, a sulfonamido, an alkylsulfonamido, an arylsulfonamido, a sulfonic ester, a urea, a phosphoryl, a nitro, -T-Q , or $-(C(R_e)(R_f))_k$-T-Q, or R_e and R_f taken together with the carbons to which they are attached form a carbonyl, a methanthial, a heterocyclic ring, a cycloalkyl group or a bridged cycloalkyl group; Q is -NO or $-NO_2$; and T is independently a covalent bond, a carbonyl, an oxygen, $-S(O)_o$- or $-N(R_a)R_i$-, wherein o is an integer from 0 to 2, R_a is a lone pair of electrons, a hydrogen or an alkyl group; R_i is a hydrogen, an alkyl, an aryl, an alkylcarboxylic acid, an aryl carboxylic acid, an alkylcarboxylic ester, an arylcarboxylic ester, an alkylcarboxamido, an arylcarboxamido, an alkylaryl, an alkylsulfinyl, an alkylsulfonyl, an arylsulfinyl, an arylsulfonyl, a sulfonamido, a carboxamido, a carboxylic ester, an amino alkyl, an amino aryl, $-CH_2-C(T-Q)(R_e)(R_f)$, or $-(N_2O_2-)\bullet M^+$, wherein M^+ is an organic or inorganic cation; with the proviso that when R_i is $-CH_2-C(T-Q)(R_e)(R_f)$ or $-(N_2O_2-)\bullet M^+$; then "-T-Q" can be a hydrogen, an alkyl group, an alkoxyalkyl group, an aminoalkyl group, a hydroxy group or an aryl group.

33. The method of claim 23, wherein the at least one compound that donates, transfers, or releases nitric oxide, or induces the production of endogenous nitric oxide or endothelium-derived relaxing factor, or is a substrate for nitric oxide synthase is L-arginine, L-homoarginine, N-hydroxy-L-arginine, nitrosated L-arginine, nitrosylated L-arginine, nitrosated N-hydroxy-L-arginine, nitrosylated N-hydroxy-L-arginine, citrulline, ornithine, glutamine, lysine, polypeptides comprising at least one of these amino acids or an inhibitor of the enzyme arginase.

34. The method of claim 23, wherein the at least one compound that donates, transfers, or releases nitric oxide, or induces the production of endogenous nitric oxide or endothelium-derived relaxing factor, or is a substrate for nitric oxide synthase is:

(i) a compound that comprises at least one ON-O-, ON-N- or ON-C- group;

(ii) a compound that comprises at least one O_2N-O-, O_2N-N-, O_2N-S- or O_2N-C-

group;

(iii) a N-oxo-N-nitrosoamine having the formula: R^1R^2N-N(O-M^+)-NO, wherein R^1 and R^2 are each independently a polypeptide, an amino acid, a sugar, an oligonucleotide, a straight or branched, saturated or unsaturated, aliphatic or aromatic, substituted or unsubstituted hydrocarbon, or a heterocyclic group, and M^+ is an organic or inorganic cation.

35. The method of claim 34, wherein the compound comprising at least one ON-O-, ON-N- or ON-C- group is an ON-O-polypeptide, an ON-N-polypeptide, an ON-C-polypeptide, an ON-O-amino acid, an ON-N-amino acid, an ON-C-amino acid, an ON-O-sugar, an ON-N-sugar, an ON-C-sugar, an ON-O-oligonucleotide, an ON-N-oligonucleotide, an ON-C-oligonucleotide, a straight or branched, saturated or unsaturated, substituted or unsubstituted, aliphatic or aromatic ON-O-hydrocarbon, a straight or branched, saturated or unsaturated, substituted or unsubstituted, aliphatic or aromatic ON-N-hydrocarbon, a straight or branched, saturated or unsaturated, substituted or unsubstituted, aliphatic or aromatic ON-C-hydrocarbon, an ON-O-heterocyclic compound, an ON-N-heterocyclic compound or a ON-C-heterocyclic compound.

36. The method of claim 34, wherein compound comprising at least one O_2N-O-, O_2N-N-, O_2N-S- or O_2N-C- group is an O_2N-O-polypeptide, an O_2N-N-polypeptide, an O_2N-S-polypeptide, an O_2N-C-polypeptide, an O_2N-O-amino acid, O_2N-N-amino acid, O_2N-S-amino acid, an O_2N-C-amino acid, an O_2N-O-sugar, an O_2N-N-sugar, O_2N-S-sugar, an O_2N-C-sugar, an O_2N-O-oligonucleotide, an O_2N-N-oligonucleotide, an O_2N-S-oligonucleotide, an O_2N-C-oligonucleotide, a straight or branched, saturated or unsaturated, aliphatic or aromatic, substituted or unsubstituted O_2N-O-hydrocarbon, a straight or branched, saturated or unsaturated, aliphatic or aromatic, substituted or unsubstituted O_2N-N-hydrocarbon, a straight or branched, saturated or unsaturated, aliphatic or aromatic, substituted or unsubstituted O_2N-S-hydrocarbon, a straight or branched, saturated or unsaturated, aliphatic or aromatic, substituted or unsubstituted O_2N-C-hydrocarbon, an O_2N-O-heterocyclic compound, an O_2N-N-heterocyclic compound, an O_2N-S-heterocyclic compound or an O_2N-C-heterocyclic compound.

37. The method of claim 36, wherein compound comprising at least one O_2N-O-, O_2N-N-, O_2N-S- or O_2N-C- group is isosorbide mononitrate and/or isosorbide dinitrate.